6.04 LEUPRORELIN ACETATE, Suspension for subcutaneous injection (modified release) containing 45 mg leuprorelin acetate, injection set, Eligard® 6 month, Mundipharma Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested PBS listing for leuprorelin acetate 45 mg syringe (Eligard 6 month®) for the treatment of central precocious puberty (CPP). The proposed main comparator was a prefilled dual chamber (PDS) leuprorelin acetate 30 mg depot injection (Lucrin Depot Paediatric 30 mg PDS®, herein referred to as "Lucrin Paediatric"). Triptorelin embonate (Diphereline®), a gonadotropin-releasing hormone (GnRH) analogue, was proposed as a secondary comparator.

1.2 Listing was requested based on a cost-minimisation approach against the least costly medicine on the PBS for the treatment of CPP, Diphereline. The submission requested a price that equals the current price of Eligard 6 month for the prostate cancer indication, noting that this price is lower than the price of Diphereline for the CPP indication.

1.3 The submission presented four 'key reasons' as to how this preparation of leuprorelin meets an unmet clinical need in patients with CPP, including that Eligard 6 month:

(1) provides longer lasting treatment compared to Lucrin Paediatric;

(2) is administered less frequently compared to Lucrin Paediatric;

(3) provides an alternative leuprorelin acetate depot product for children with CPP in case of medication shortages on the PBS; and

(4) is administered by a less painful subcutaneous injection compared to Lucrin Paediatric which is an intramuscular injection.

1.4 The submission, however, did not supply any empirical evidence to support the claim that it was inappropriate to switch between leuprorelin acetate depot products and Diphereline during a medication shortage. However, in its July 2021 consideration of triptorelin, the PBAC considered that flexibility in the restrictions for leuprorelin and triptorelin to allow for switching between GnRH analogues in continuing therapy was reasonable. Additionally, the percentage of adverse events related to injection pain appeared to be higher in the Eligard 6-month trial, compared to the trial of Lucrin Paediatric (see the Comparative harms).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Central Precocious Puberty (CPP) in girls 10 years or younger or boys 11 years or younger.
Intervention	Leuprorelin acetate modified release injection syringe (Eligard 6 month), administered every 6 months as a single subcutaneous injection.
Comparator	Leuprorelin acetate 30 mg modified release injection syringe (Lucrin Paediatric), administered every 3 months via intramuscular injection.
Outcomes	Primary Percentage of children with luteinising hormone suppression (LH) (<4 IU/L) at week 24. Secondary Percentage of children with LH suppression (<4 IU/L) at week 12, 36, week 48. Mean LH levels across timepoints, post stimulation test. LH, follicle stimulating hormone (FSH), basal oestradiol (in girls) and testosterone (in boys) levels at baseline, on-treatment, end-of treatment, and corresponding changes from baseline, percent responders with suppression of hormone levels. Change in height and growth velocity, sexual maturation, and testicular volume in boys, percent with suppression. Adverse events.
Clinical Claim	For the treatment of central precocious puberty, leuprorelin modified release 6 month injection (leuprorelin acetate 45 mg) is non-inferior compared to leuprorelin depot paediatric 30 mg PDS IM (administered to cover 6 months treatment) at suppression with respect to luteinising hormone levels with a comparable safety profile.

Source: Table 1-1, p11 of the submission.
Note: Table 1-1 in the submission prefers to CPP as Chronic Precocious Puberty. The error is corrected here.
CPP, Central Precocious Puberty; LH, luteinising hormone; FSH, follicle stimulating hormone; IM, intramuscular injection

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's overview was available.

2.2 The proposed indication in the draft product information (PI) is 'Eligard 6 month is indicated for the treatment of children with central precocious puberty.' This was consistent with the requested listing; however, the requested listing included additional age criteria, consistent with the Lucrin Paediatric listing.

Previous PBAC consideration

2.3 This is the first submission for Eligard 6 month for the CPP indication. The first leuprorelin listing for the treatment of CPP was Lucrin Paediatric (listed in December 2015). Currently, both the Eligard 6 month and Lucrin Paediatric brands of leuprorelin are PBS listed for locally advanced or metastatic carcinoma of the prostate. Diphereline (triptorelin embonate) was recommended for the treatment of CPP at the July 2021 PBAC meeting and listed in November 2021.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
LEUPRORELIN Suspension for subcutaneous injection (modified release) containing leuprorelin acetate 45mg, injection set	1	1	$1,750.56	Eligard 6 month	Mundipharma Pty Ltd

Category/Program:	General Schedule
PBS indication:	Central precocious puberty
Treatment phase:	Initial and continuing
Restriction:	Restricted benefit
Treatment criteria:	Must be treated by a paediatric endocrinologist; OR Must be treated by an endocrinologist specialising in paediatrics OR Must be treated by at least one of: (i) a paediatric endocrinologist, (ii) an endocrinologist specialising in paediatrics; or Must be treated by a medical practitioner who has consulted one of the above-mentioned specialist types, with agreement reached that treatment continue with this drug on this occasion. AND Patient must be undergoing continuing treatment with a gonadotropin releasing hormone analogue initiated through the PBS for this PBS indication.
Population criteria: (initiation)	Patient must be aged 10 years or younger (girls) or 11 years or younger (boys), AND Patient must have had an onset of central precocious puberty before 8 years (girls) or 9 years (boys).

Source: Table 1-5, 1-6, 1-7, p20-21 of the submission.

3.1 The submission requested a restricted benefit listing for Eligard 6 month that was similar to the comparator Lucrin Paediatric. The submission claimed that treatment would be ongoing until the patient reaches puberty. The restriction for Eligard 6 month is different from that of Diphereline, where a patient must be aged 12 years or younger (girls) or 13 years or younger (boys), and the patient must have had an onset of CPP before 9 years (girls) or 10 years (boys). In its July 2021 consideration of Diphereline, the PBAC considered the differences in age ranges between triptorelin and leuprorelin in the registration studies were unlikely to substantially impact clinical practice and it was reasonable for the restrictions to reflect the upper subject age ranges in the TGA registration studies (paragraph 7.7, triptorelin July 2021 PBAC Public Summary Document (PSD)).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Precocious puberty is defined as "the development of puberty younger than that which is expected for ethnicity and race"[1]. Puberty is considered early if it commences prior to 8 years in Caucasian girls and 9 years in boys; in Hispanic and African American girls the cut-off is younger at 7.5 years[1]. CPP is caused by early maturation of the hypothalamic-pituitary-gonadal (HPG) axis, with the initial clinical signs of breast development in girls and testicular enlargement in boys[2]. Children with CPP have accelerated linear growth for their age, an advanced bone age and pubertal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[2]. CPP has an incidence of 1 in 5,000-to-10,000 children[3] with a female to male ratio of about 20:1[4]. The drug utilisation sub-committee (DUSC) estimated that in Australia between 2014 to 2018 there were a total of 711 patients with CPP (102 male patients and 609 female patients) using leuprorelin paediatric (DUSC 2019).

4.2 The aims of treatment are to arrest physical maturation, prevent early menarche, bring final adult height closer to genetic expectation, and allow normal psychosocial development (National Organization for Rare Disorders 2021). The submission did not anticipate changes to the clinical treatment algorithm (including age of commencement and discontinuation) for Eligard 6 month and Lucrin Paediatric.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated leuprorelin acetate 30 mg modified release injection (Lucrin Paediatric) as the main comparator. The main arguments provided in support of this nomination were that both Lucrin Paediatric and Eligard 6 month have the same ATC code (L02AE02) and are pharmacologically the same with the same mode of action. Lucrin Paediatric is the only leuprorelin acetate product that is PBS listed for the treatment of CPP (item 11944P, 11960L). The PBAC considered that Lucrin Paediatric was an appropriate comparator.

5.2 The submission also nominated Diphereline, a GnRH analogue, as a supplementary comparator. Diphereline was recommended for the treatment of CPP at the July 2021 PBAC meeting and listed in November 2021. It is administered as a depot intramuscular injection every 6 months. The submission argued that Diphereline was not the main comparator because it did not contain leuprorelin acetate and

[1] Aguirre, Rebecca Schneider, and Erica A. Eugster. "Central precocious puberty: From genetics to treatment." Best Practice & Research Clinical Endocrinology & Metabolism 32.4 (2018): 343-354.
[2] Cantas-Orsdemir, Sena, and Erica A. Eugster. "Update on central precocious puberty: from etiologies to outcomes." Expert Review of Endocrinology & Metabolism 14.2 (2019): 123-130.
[3] Eugster, Erica A. "Treatment of central precocious puberty." Journal of the Endocrine Society 3.5 (2019): 965-972.
[4] National Organization for Rare Disorders (2021). "Precocious Puberty." Available at: https://rarediseases.org/rare-diseases/precocious-puberty/

had limited PBS usage at the time of the Eligard 6 month submission. The PBAC accepted Diphereline (triptorelin) as a supplementary comparator.

5.3 Under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. Given the PBAC has previously considered that triptorelin is of non-inferior comparative effectiveness and safety to leuprorelin for the treatment of CPP, forms of both leuprorelin and triptorelin listed for this indication are considered relevant alternative therapies. Based on the recent price reduction of Lucrin Paediatric (AEMP = $845.46), the annualised (direct treatment) cost for Diphereline (used every 6 months) and Lucrin Paediatric (used every 3 months) are the same (approximately $3,381) (discussed further in the Economic analysis section).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on a naïve indirect comparison consisting of:

- one open label, single arm, multicentre study of Eligard 6 month (TOL2581A, N=64), leuprorelin administered at 45 mg every 6 months;
- one open label, phase 3, randomised, multicentre study of Lucrin Paediatric (Lee 2012, N=84) and its extension study (Lee 2014, N=72), leuprorelin administered at 30 mg every 3 months;
- one open label, single arm, multicentre study of Diphereline (Study 301, N=44), triptorelin embonate administered at 22.5 mg every 6 months.

6.4 The details of the trials presented in the submission are provided in Table 2 below.

Table 2: Trials and associated reports presented in the submission

Study identifier (ID)	Key data sources: Clinical Study Reports (CSR) or key publication	Publication citation
Eligard 6 month study		

Study identifier (ID)	Key data sources: Clinical Study Reports (CSR) or key publication	Publication citation
TOL2581A	Tolmar Inc. An Open-label, Single Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate for Injectable Suspension Controlled Release in Subjects with Central (Gonadotropin-Dependent) Precocious Puberty. 12 March 2021. (Tolmar Inc 2021)	CSR – key data source
	Tolmar Inc (2018). TOL2581A: Appendix 16.1.9 Documentation of Statistical Methods, Tolmar Inc,. (Tolmar Inc 2018)	CSR Statistical Analysis Plan – key data source
	Klein, KO, Freire, A, et al. (2020). "Phase 3 Trial of a Small-volume Subcutaneous 6-Month Duration Leuprolide Acetate Treatment for Central Precocious Puberty." The Journal of clinical endocrinology and metabolism 105(10). (Klein, Freire et al. 2020)	Key full study publication
	Klein, KO, Dragnic, S, et al. (2018). "Predictors of bone maturation, growth rate and adult height in children with central precocious puberty treated with depot leuprolide acetate." Journal of pediatric endocrinology & metabolism: JPEM 31(6): 655-663. (Klein, Dragnic et al. 2018)	Additional publication. Post hoc analyses.
	NCT02452931. "Study of Leuprolide Acetate Injectable Suspension in the Treatment of Central Precocious Puberty." ClinTrials listing. (Tolmar Inc 2020)	ClinTrials listing of TOL2581A
Comparator - Lucrin Paediatric		
Lee 2012	Lee, PA, Klein, K, et al. (2012). "Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty." The Journal of clinical endocrinology and metabolism 97(5): 1572-1580. (Lee, Klein et al. 2012)	Key comparator study publication.
	NCT00635817. "A Study of Leuprolide 11.25 mg and 30 mg Administered Every 3 Months to Treat Central Precocious Puberty " ClinTrials listing. (Abbott 2011)	ClinTrials listing of Lee 2012
	Klein, K, Mauras, N, et al. (2010). "Treatment of central precocious puberty with leuprolide acetate 3 Month depot 11.25 or 30 mg: A U.S. Multicenter Study." Hormone Research in Paediatrics 74(SUPPL. 3): 150. (Klein, Mauras et al. 2010)	Abstract publication of Lee 2012
Lee 2014	Lee, PA, Klein, K, et al. (2014). "36-month treatment experience of two doses of leuprolide acetate 3-month depot for children with central precocious puberty." The Journal of clinical endocrinology and metabolism 99(9): 3153-3159. (Lee, Klein et al. 2014)	Extension study of Lee 2012
	NCT00667446. "Safety Extension Study Of Leuprolide Acetate (Lupron Depot) In The Treatment Of Central Precocious Puberty". ClinTrials listing. (AbbVie (prior sponsor Abbott) 2014)	ClinTrials listing of Lee 2014
Comparator – Diphereline		
Study 301	Klein, Karen, et al. "Efficacy and safety of triptorelin 6-month formulation in patients with central precocious puberty." Journal of Pediatric Endocrinology and Metabolism 29.11 (2016): 1241-1248.	Supplementary comparator study publication
	NCT01467882. "Efficacy, Safety, and Pharmacokinetics (PK) of Triptorelin 6-month Formulation in Patients With Central Precocious Puberty". ClinTrials listing. (Debiopharm International SA 2017)	ClinTrials listing (Debiopharm International SA 2017)

Source: Table 2-4, p26 of the submission, and text and references in the supplementary information.

6.5 The key features of the trials are summarised in Table 3.

Table 3: Key features of the included trials

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
Eligard 6 month (leuprorelin acetate) 45 mg depot					
TOL2581A	62	SAS, OL, MC 48 week	High	CPP	Primary: % responders (defined as serum LHC <4 IU/L 30 min after GnRHa agonist stimulation) at Week 24. Secondary: • % responders at all study visits • Mean serum LH (IU/L) post stimulation GnRHa stimulation at study visits • Ratio of bone age to chronological age. • Growth velocity (cm/year) • % patients with response in serum oestradiol and testosterone • Height (cm) at each timepoint • Mean HC of FSH, oestradiol and testosterone post stimulation at study visits • Changes in Tanner category from baseline to end of study • Menses presence and change • PK outcomes for serum leuprorelin at each study visit Safety: TEAEs, treatment related TEAEs, individual TEAE and SOC TEAE rates
Lucrin Paediatric					
Lee 2012	42	MC, R, OL, 36 week	High	CPP	Primary: % patients with serum LH concentration <4 IU/L, months 2 to 6. Secondary: • % patients with suppression of basal oestradiol <20 pg/mL • % participants with suppression of testosterone in <30 ng/dL • Peak-stimulated LHC by visit • % participants with suppression of the physical signs of puberty • Change from baseline in incremental growth rate • Ratio of change from baseline in bone age/Change from baseline in chronological age Safety: Treatment-emergent AEs; Serious AEs; and SOC TEAEs

Lee 2014	38	MC, R, OL, 144 week	High	CPP	Primary: % patients with serum LH concentration <4 IU/L at month 6, 12, 24 and 36. Secondary: • Mean peak simulated LHC • % girls with suppression of basal oestradiol • Number and % girls and boys with suppression of physical signs of puberty • Change from baseline growth rate • Ratio of change from baseline in bone age/ change from baseline in chronological age Safety: TEAEs
Diphereline					
Study 301	44	SAS, OL, 50 week max follow-up	High	CPP	Primary: % responders (defined as LHC to <5 IU/L 30 minutes after GnRH agonist stimulation) at Month 6 (Day 169). Exploratory analysis: LH suppression <4 IU/L. Secondary: • % responders at all study visits. Exploratory analysis: Used LH suppression <4 IU/L. • Mean serum LH (IU/L) post stimulation GnRHa stimulation at study visits • Ratio of bone age to chronological age. • Growth velocity measured from baseline. • % patients with response in serum oestradiol and testosterone. Safety: TEAEs, treatment related TEAEs, individual TEAE and SOC TEAE rates

Source: Table 2-11, p42 of the submission; Table 1-1, Table 2-1, p2 and Table 3-1, p3 of the supplemental information; text in p81-84 of the submission; text and tables in Lee 2014.

AE, adverse event; CPP, central precocious puberty; FSH, follicle stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist; HC, hormone concentration; LH, luteinising hormone; LHC, luteinising hormone concentration; MC, multi-centre; OL, open label; OS, overall survival; SAS, single arm study; R, randomised; TEAE, treatment-emergent adverse event; SOC, system order class;

6.6 All included studies had a high risk of bias. Both TOL2581A (Eligard 6 month) and Study 301 (Diphereline) were single arm, non-randomised, non-comparative studies while Lee 2012 was a randomised, open label, dose finding study, and Lee 2014 was Lee 2012's extension study.

6.7 The submission compared the population, disease, circumstances and treatments in the TOL2581A setting and the Australian setting. The submission claimed that the use of Eligard 6 month would be generally consistent with use in Australian children with CPP.

6.8 There were concerns regarding the sample size of male participants in the key trials. In the trial of TOL2581A (Eligard 6 month), the ratio of females to males in the ITT population was 60 to 2 participants (30:1). In the trial of Lee 2012 (Lucrin Paediatric), of the treatment naïve patients (N=21), which was the population more comparable to the population in the trial of Eligard 6 month, there were 19 girls and 2 boys (a ratio of 9.5:1, NCT00635817). The submission noted that during the period 2014-2018, there were a total of 711 children in Australia with CPP, as estimated by the DUSC (2019). The ratio of females to males was 609 to 102 (6:1). The ratios of females to males in the trials were different to those of Australian children. Furthermore, the low numbers of boys in either trial leads to high uncertainty in conclusions regarding the efficacy and safety in the treatment of boys with CPP, especially the durability of effect out to 6 months in one injection. It is noteworthy that the TGA's Round 2 Clinical evaluation report also noted that the low male numbers with CPP included in the TOL2581A was a concern (Round 2 Clinical evaluation report). The Pre-Sub-Committee Response (PSCR) stated that the Updated TGA Delegates Overview notes that extrapolation of evidence from females to males is possible because the underlying mechanism of CPP is the same for both sexes, and suppression of LH is a direct measure of the pharmacological effect of leuprolide on the HPG-axis, regardless of sex. The ESC noted that the clinical evaluator considered this extrapolation to be satisfactory in the Round 2 Clinical evaluation report and considered this was reasonable.

6.9 Additionally, there were applicability concerns regarding representation by race and ethnicity in the trials. In TOL2581A, the ratio of Hispanic or Latino participants to non-Hispanic or Latino was 35:27 (participants). This ratio is likely far greater than those in Australia as <5% of the Australian population are identified as Hispanic/Latino[5]. Precocious puberty is defined as the development of puberty younger than that which is expected for ethnicity and race" and the defined age cut-off for early commencement is younger in Hispanic girls than Caucasian girls[6].

6.10 The treatment details in the included trials are shown in Table 4.

[5] According to the ABS, the percentage of Australians born in South American countries were around 2%; and about 5% of Australian identified as "other ethnicity" which include Hispanic and Latino. See https://www.abs.gov.au/ausstats/

[6] Aguirre, Rebecca Schneider, and Erica A. Eugster. "Central precocious puberty: From genetics to treatment." Best Practice & Research Clinical Endocrinology & Metabolism 32.4 (2018): 343-354.

Table 4: Interventions compared in the studies

Treatment	Dosage regimen	Duration of treatment maximum months	Duration of follow-up maximum months
TOL2581A			
Leuprorelin acetate 45mg (Eligard 6 month)	45 mg extended-release formulation administered as a SC injection into the abdominal area at Day 0 and Month 6.	6 months	6 months
Lee (2012)			
Leuprorelin acetate 30 mg (Lucrin Paediatric)	30 mg depot administered IM 3 months apart.	6 months	3 months
Lee (2014)			
Leuprorelin acetate 30 mg (Lucrin Paediatric)	30 mg depot administered IM 3 months apart. First dose was administered on study day 1 which was month 6 of the Lee 2012 lead-in study.	36 months	3 months
Study 301			
Triptorelin embonate 22.5 mg (Diphereline)	22.5 mg triptorelin administered every 24 weeks as a single intramuscular injection	6 months	6 months

Source: Table 2-11, p42 of the submission; Table 1-1, p2 and Table 3-1, p3 of the supplemental information.

6.11 The dose and frequency of Eligard 6 month in TOL2581A, Lucrin Paediatric in Lee (2012/2014), and Diphereline in Study 301 were consistent with their respective proposed/approved TGA PI documents.

6.12 The treatment durations in these studies were substantially shorter than the average expected duration of treatment with gonadotropin-releasing hormone agonist (GnRHa), and what would be allowed in the respective indications and restrictions. Lee (2014) indicated that most patients discontinued due to the individual being ready to progress through puberty (28 out of 48 discontinuations), suggesting that median treatment duration in the extension was up to three years. However, treatment duration of >3 years with GnRHa has been reported in the literature[7].

Comparative effectiveness

6.13 The results of the trial are shown in Table 5 and Table 6.

Table 5: LH response (LH <4 IU/L) (ITT populations)

	TOL2581A		Lee 2012		Study 301	
Timepoint	**Eligard 6 month (N=62)**		**Lucrin Paediatric Treatment naïve population (N=21)** [(e)]		**Diphereline 22.5 mg (N=44)** [(a)]	
	n/N	**% responders (95% CI)**	**n/N**	**% responders (95% CI)**	**n/N**	**% responders (95% CI)**
Week 8 /	-	**-**	Months 2-6:	Months 2-6:	42/44	95.45 (84.53, 99.44)

7 Krishna, Kanthi Bangalore, et al. "Use of gonadotropin-releasing hormone analogs in children: update by an international consortium." Hormone research in paediatrics 91.6 (2019): 357-372.

	TOL2581A		Lee 2012		Study 301	
Timepoint	**Eligard 6 month (N=62)**		**Lucrin Paediatric Treatment naïve population (N=21)** [e]		**Diphereline 22.5 mg (N=44)** [a]	
	n/N	**% responders (95% CI)**	**n/N**	**% responders (95% CI)**	**n/N**	**% responders (95% CI)**
Month 2			19/21	Pre-specified: 90.5 (77.9, 100.0) [c] Post hoc: 90.5 (69.6, 98.8) [d]		
Week 12 / Month 3	51/60	85.0 (76.0, 94.0) [b] [c]			41/44	93.18 (81.34, 98.57)
Week 24 / Month 6	54/62	87.1 (78.8, 95.4) [b] [c] 87.1 [b] (76.2, 94.3) [b] [d]			40/44	90.91 (78.33. 97.47) [d]
Risk Difference (vs Eligard 6 month) at week 24:			-3.4% (95% CI: -18.5, 11.7) p=0.6604.		-3.8% (95% CI: -15.7, 8.1) p=0.5303	
Week 36 / Month 9	50/59	84.7 (75.6, 93.9) [c]			41/44	93.18 (81.34, 98.57)
Week 48 / Month 12	50/58	86.2 (77.7, 95.1) [c]			43/44	97.73 (87.98, 99.94)

Source: Table 2-37, p87 of the submission; Table 5-1, p9 of the supplemental information; text and tables in Lee 2012; text, p86 of the submission; text, p8 of the supplementary information.
(a) The submission stated that the data was for the "percentage of patients with LH below 4IU/L at 6 month), and that it was an exploratory analysis. See discussion in paragraph 6.12 below.
(b) 95% CIs calculated for submission, not reported in CSR.
(c) 95% CIs calculated using consistent methodology: life table method (Lee 2012) / normal approximation to the binomial calculation (TOL2581A)
(d) 95% CIs calculated using binomial exact method
(e) The whole trial sample was 84 (children) but the sample treated with Lucrin Paediatric was 42 children, and the treatment naïve population was 21

6.14 The absolute percentages of responders to Eligard 6 month at 2 months and 6 months was lower than that of Lucrin Paediatric assessed within the time frame of 2 and 6 months. Similarly, the absolute percentages of responders to Eligard 6 month were lower than those of Diphereline for the same time frame of 2 months and 6 months. The indirect comparison estimates, however, showed no statistically significant difference in the risk differences between Eligard 6 month and each of the comparators. It was noted that the percentage of responders (with LH below 4 IU/L) presented in the submission was only an exploratory analysis and cannot be verified. The primary outcome for Study 301, as reported in the respective publications, is "percentage of patients with LH below 5 IU/L at month 6" (as opposed to below 4 IU/L in TOL2581A and Lee 2012).

Table 6: Comparison of mean peak stimulated LH levels across studies

	TOL2581A	Study 301	Lee 2012
	Eligard 6 month	**Diphereline 22.5 mg**	**Lucrin Paediatric - Treatment Naïve**
Mean luteinising hormone level across time points (95% CI)	2.27 (1.52, 3.02) [a]	2.37 (1.44, 3.29)	1.73 (1.29, 2.16)

		TOL2581A	Study 301	Lee 2012
		Eligard 6 month	Diphereline 22.5 mg	Lucrin Paediatric - Treatment Naïve
Pre-study/baseline	N Mean (SD)	62 27.45 (31.389)	44 27.21 (20.56)	21 23.5 (16.76)
Week 4 / Month 1	N Mean (SD)	60 0.78 (1.579)	44 2.00 (2.94)	21 1.9 (1.74)
Week 8 / Month 2	N Mean (SD)	NA	44 1.96 (4.43)	21 2.0 (2.25)
Week 12 / Month 3	N Mean (SD)	60 3.07 (5.913)	44 2.04 (1.45)	20 1.4 (0.78)
Week 24 / Month 6	N Mean (SD)	62 2.97 (6.159)	44 4.16 (12.26)	18 1.6 (0.95)
Week 36 / Month 9	N Mean (SD)	59 2.26 (1.779)	44 1.97 (1.42)	NA
Week 48 / Month 12	N Mean (SD)	58 2.29 (1.584)	44 2.06 (1.61)	NA

Source: Table 2-38, p88 of the submission; Table 5-2, p10 of the supplementary information.
NA, not applicable; SD, standard deviation; LH, luteinising hormone
Peak stimulated levels measured at 30 minutes post GnRHa administration.
(a) 95% CIs calculated in Attachment 3 (University of Melbourne, Statistical Consulting Centre Report)

6.15 The submission noted that the comparison showed similar mean levels across the timepoints for Eligard 6 month and Lucrin Paediatric. The calculated mean serum level at 2.27 (95% CI 1.52, 3.02) was slightly lower for Eligard 6 month than for Diphereline (2.37, 95% CI 1.44, 3.29). The LH level in TOL2581A did not increase above the cut-off value of 4 IU/L at any study visit, while in Study 301 a mean value above 4 was reported at Week 24. This was mainly due to one patient who had an LH value increased to 83 IU/L at Month 6, which was due to a technical malfunction with the first injection, but dropped to 3.2 at Month 9, following a successful second injection. All the mean values in Study 301 at Month 3, Month 9, and Month 12 were lower than in TOL2581A. In addition, the mean value in Lee 2012 (1.73) was lower than in TOL2581A (2.27) which difference was 0.54, but the mean value in Study 301 (2.37) was only slightly higher than in TOL2581A. Due to the very small sample size, the values could fluctuate widely, and therefore, the comparative conclusion based on the observed trends was uncertain.

Comparative harms

6.16 The adverse events as reported in the trial are shown in Table 7 below.

Table 7: Summary of key adverse events in trials

	TOL2581A	Study 301	Lee 2012		Lee 2014
AE n (%) of patients	**Eligard 6 month (N=64)**	**Diphereline 22.5 mg (N=44)**	**Lucrin Paediatric Treatment Naïve (N=21)**	**Lucrin Paediatric Previously Treated (N=21)**	**Lucrin Paediatric (N=38)**
Any TEAE	53 (83%)	33 (75%)	15 (71%)	17 (81%)	34 (90%)
Treatment-related AE	22 (34%)	4 (9.1%)	NA	NA	8 (21%)
Blood and lymphatic system disorders	0 (0%)	NA	NA	≥2 (10%)	NA
Ear and labyrinth disorders	0 (0%)	NA	NA	≥2 (10%)	2 (5%)
Endocrine disorders	1 (2%)	NA	2 (10%)	NR	NR
Gastrointestinal disorders	21 (33%)	5 (11%)	4 (19%)	1 (5%)	14 (37%)
Infections and infestations	32 (50%)	21 (48%)	5 (24%)	3 (14%)	18 (53%)
Injury, poisoning and procedural complications	11 (17%)*	NR	NA	2 (10%)	4 (11%)
Investigations	3 (5%)*	NA	2 (10%)	1 (5%)	3 (8%)
Musculoskeletal and connective tissue disorders	3 (5%)	NA	1 (5%)	2 (10%)	8 (21%)
Nervous system disorders	13 (20%)	6 (14%)	8 (38%)	6 (29%)	6 (16%)
Psychiatric disorders	3 (5%)	NA	2 (10%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	22 (34%)	3 (7%)	6 (29%)	11 (52%)	17 (45%)
General disorders	35 (55%)	5 (11%)	6 (29%)	13 (62%)	14 (41%)
Injection Site Pain	20 (31%)	1 (2%)	4 (19%)	7 (33%)	9 (24%)
Injection site erythema	6 (9%)	NA	NA	NA	NA
Pyrexia	11 (17%)	NR	2 (10%)	6 (29%)	5 (13%)

Source: Table 2-42, p93-94 of the submission; Table 5-5, p14-16 of the supplemental information.
NA, not available; SOC, system organ class; TEAE, treatment-emergent AE
* No individual AE reported in more than 5% of patients in this SOC
SOC: Injury, poisoning and procedural complications not included as data not available for Lee 2012 and Lee 2014 and in TOL2581A no single TEAE was reported in >5% patients. Note this SOC includes arthropod bite, concussion, contusion, fall, foot fracture etc. that are likely mainly related to childhood injuries. Details are fully reported in Table 2.42.

6.17 The number of adverse events appear to be unfavourable to Eligard 6 month compared to Lucrin Paediatric in the naïve treatment arm, however, the trends appear to favour Eligard 6 month when comparing to Lee 2014 extension, noting that the patients in the Lee 2014 were treatment experienced. Given the high risk of bias of all included studies and that they were all single arm studies, the comparison was uncertain.

6.18 The submission claimed that the administration of Eligard 6 month via subcutaneous injection would be less painful compared to Lucrin Paediatric which is administered via intramuscular injection. This was not adequately supported by the trial data: injection site pain was reported at 31% in TOL2581A (Eligard 6 month) compared to 19% (treatment-naïve patients) and 33% (previously treated patients) in Lee 2012 (Lucrin Paediatric).

Clinical claim

6.19 The submission described Eligard 6 month as non-inferior in terms of effectiveness and safety compared with Lucrin Paediatric. The submission also described Eligard 6 month as non-inferior in terms of effectiveness and safety compared with Diphereline. Both claims were based on numerical trends in a naïve comparison of the single treatment arms of different studies with a high risk of bias. Consequently, the evaluation considered that the reliability of these claims was not strong, however, as the PBAC has previously accepted the non-inferiority of Diphereline compared to Lucrin Depot Paediatric 30 mg with an equivalent level of evidence (PBAC triptorelin PSD July 2021)[8], it may be reasonable to extend the equivalence to Eligard 6 month.

6.20 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonably supported by the data.

Economic analysis

6.21 The submission presented a cost-minimisation approach. The key assumptions and components of the cost-minimisation approach are summarised in Table 8.

Table 8: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the Comparative Effective and Clinical Claim sections, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented in the Comparative Harm and Clinical Claim sections, safety is assumed to be non-inferior
Evidence base	Naïve treatment comparison of TOL2581A (Eligard 6 month) versus Lee 2012 and Lee 2014 (Lucrin Paediatric) Naïve treatment comparison of TOL2581A (Eligard 6 month) versus Study 301 (Diphereline)
Equi-effective doses	2 injections of Eligard 6 month (45 mg) were equi-effective to 4 injections of Lucrin Paediatric. 2 injections of Eligard 6 month (45 mg) were equi-effective to 2 injections of Diphereline
Direct medicine costs	Eligard 6 month costs less than Lucrin Paediatric in terms of price per year
Other costs or cost offsets	None Eligard 6 month has a similar administration route to Lucrin Paediatric and Diphereline. Other costs are expected to be equivalent.

Source: Table 3-1, p99; Table 3-2, p102; Text compiled from submission, p99-102 of the submission.
AE, adverse event; MBS, Medicare Benefits Schedule

6.22 The submission requested a price consistent with the current price of Eligard 6 month for the prostate cancer indication (AEMP $1,606.32).

[8] PBAC PSD (2021). Triptorelin, Powder for I.M. injection (prolonged release) 22.5 mg (as embonate) with solvent, syringe and needles, Diphereline, PBAC.

6.23 The submission did not explicitly present the equi-effective doses. Based on the presented cost-minimisation analysis, the implied equi-effective doses over a 1-year period were:

2 injections of Eligard 6 month (45 mg) ≡ 4 injections of Lucrin Paediatric

2 injections of Eligard 6 month (45 mg) ≡ 2 injections of Diphereline (22.5 mg)

6.24 The equi-effective doses used in the cost-minimisation approach were consistent with the key trials (TOL2581A, Lee 2012, Lee 2014, Study 301) and the draft PI of Eligard 6 month and approved PIs of Lucrin Paediatric and Diphereline.

6.25 No additional cost or cost offsets were included in the analysis. The submission noted that Eligard 6 month would require fewer consultations compared to Lucrin Paediatric because Lucrin Paediatric is administered every 3 months. The unit cost for consultation and biochemical tests would be identical in all treatments. This was consistent with the PBAC recommendation for Diphereline (PBAC triptorelin PSD July 2021)[9].

6.26 The results of the cost-minimisation analysis are shown in Table 9.

Table 9: Results of the cost-minimisation analysis

Treatment	AEMP	Injections per year	Annual cost per year
Eligard 6 month vs. Lucrin Paediatric			
Eligard 6 month – 45 mg of leuprorelin, 1 injection	$1,606.32	2	$3,212.64
Lucrin Paediatric, 1 injection (a)	$1,071.68	4	$4,286.72
Annual savings without cost offsets (Eligard vs Lucrin)a			$1074.08
Lucrin Paediatric, 1 injection (b)	$845.46	4	$3,381.84
Annual savings without cost offsets (Eligard vs Lucrin)b			$169.20
Eligard 6 month vs. Diphereline			
Eligard 6 month – 45 mg of leuprorelin, 1 injection	$1,606.32	2	$3,212.64
Diphereline – triptorelin 22.5 mg for injection, 1 injection	$1,690.87	2	$3,381.74
Annual savings without cost offsets (Eligard vs Diphereline)			$169.10

Source: Table 3-2, p102 of the submission.
(a) The numbers in this row were presented by the submission
(b) The numbers in this row were compiled during the evaluation; the price for Lucrin Paediatric reduced in February 2022 (AEMP = $845.46), following the listing of Diphereline in November 2021.
AEMP, approved ex-manufacturer price; mg, milligram.

6.27 In February 2022, the AEMP of Lucrin Paediatric (#11944P, 11960L) was decreased from $1,071.68 to $845.46. This was not reflected in the submission. At the proposed price, Eligard 6 month would still be the least costly, compared to Lucrin Paediatric and Diphereline.

[9] PBAC PSD (2021). Triptorelin, Powder for I.M. injection (prolonged release) 22.5 mg (as embonate) with solvent, syringe and needles, Diphereline, PBAC.

Estimated PBS usage & financial implications

6.28 This submission was not considered by DUSC. The submission used a market share approach to estimate the number of scripts of Eligard 6 month, assuming that Eligard 6 month would only substitute for Lucrin Paediatric for the treatment of CPP, giving a corresponding script reduction of 1:2. While Diphereline, the alternative therapy for CPP, was only listed in November 2021 and market share data would not have been available at the time of submission, its treatment duration is the same as Eligard 6 month (i.e. the script equivalence for these products would be 1:1). Therefore, it may not be reasonable to assume a scripts reduction ratio of 1:2 (Eligard 6 month: Lucrin Paediatric). This approach may overestimate the cost savings of listing Eligard 6 month for the treatment of CPP; however, given the annual cost of Eligard 6 month based on the requested price for the CPP indication is less than that of either Lucrin Paediatric or Diphereline, the listing would remain cost saving to the PBS in any scenario.

6.29 The key inputs for the financial estimates are shown in Table 10.

Table 10: Key inputs for financial estimates

Data	Value	Source	Comment
Market growth			
Average annual growth rate – initiation	26%	Calculated based on the historical data	The submission referred to the incorrect period, 2022-2027 instead of 2023-2028. The estimation was based on the historical data of Lucrin Paediatric for the period 2015 to 2021. The submission calculated the average annual growth rate from the scripts of two years, 2016 and 2020. An alternative method would be to calculate the annual growth rates then average them. A more accepted method of forecasting market growth is fitting prediction lines on the historical scripts. Using this method, the estimated number of scripts was substantially smaller. For instance, the predicted market share in 2027 was around one third of the submission's estimation. During the evaluation, all the calculations were re-calculated.
Average annual growth rate – continuation	21%	Calculated based on the historical data	
Average annual growth rate – total	22%	Calculated based on the historical data	
Market share – initiation [(a)]	Yr 1: [redacted] Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	Predicted scripts based on the historical data	
Market share – continuation [(a)]	Yr 1: [redacted] Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	Predicted scripts based on the historical data	
Market share – total [(a)]	Yr 1: [redacted] Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	Predicted scripts based on the historical data	
Treatment utilisation			
Uptake rate – initiation	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]%	Assumption by the Sponsor	No justification for the uptake rates.

Data	Value	Source	Comment
	Yr 6: [redacted]%		
Uptake rate – continuation	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Assumption by the Sponsor	No justification for the uptake rates.
Scripts dispensed – initiation [b]	Yr 1: [redacted][4] ([redacted][4]) Yr 2: [redacted][4] ([redacted][4]) Yr 3: [redacted][4] ([redacted][4]) Yr 4: [redacted][4] ([redacted][4]) Yr 5: [redacted][4] ([redacted][4]) Yr 6: [redacted][4] ([redacted][4])	Predicted scripts based on the historical data	These results were calculated based on the number of total services of initiation/continuation in each year. The submission made several calculation errors in the excel file. Most notably: the scripts for 11960L (initiation) and 11944P (continuation) of the year 2020 were used for the calculation of scripts in the financial year 2021, instead of using all the items 11960L and 10256T (initiation) and 11944P and 10255R (continuation), resulting in a substantially lower estimates of number of scripts. During the evaluation, all the calculations were re-calculated.
Scripts dispensed – continuation [b]	Yr 1: [redacted][4] ([redacted][4]) Yr 2: [redacted][4] ([redacted][4]) Yr 3: [redacted][4] ([redacted][4]) Yr 4: [redacted][4] ([redacted][4]) Yr 5: [redacted][4] ([redacted][4]) Yr 6: [redacted][4] ([redacted][1])	Predicted scripts based on the historical data	
Scripts dispensed – total [b]	Yr 1: [redacted][4] ([redacted][4]) Yr 2: [redacted][4] ([redacted][4]) Yr 3: [redacted][4] ([redacted][4]) Yr 4: [redacted][4] ([redacted][1]) Yr 5: [redacted][4] ([redacted][1]) Yr 6: [redacted][4] ([redacted][1])	Predicted scripts based on the historical data	
Costs			
Eligard 6 month AEMP	$1,606.32	Requested price	Checked. Consistent with the Background section (above)
Eligard 6 month DPMQ	$1,750.56		
Leuprorelin 30mg AEMP	$1,071.68 (*$845.46*)	PBS items: 11960L, 11944P	Lucrin Paediatric was subject to a price reduction on 1 February 2022. The DPMQ is $951.64 listed on the PBS (or AEMP = 845.46)
Leuprorelin 30mg DPMQ	$1,186.76 *($951.64)*		

Source: Financial estimate spreadsheet of submission, 'Eligard - Leuprorelin - CPP - Financial Estimates - Base Case - 28 Feb 2022' and during the evaluation

(a) The submission estimated the number of scripts for the period 2022-2027 (in the excel file) but did not use them as inputs for the market growth rate. Instead, they recalculated the scripts and referred to the incorrect number of scripts for 2020 (see below)

(b) Numbers in brackets and in italic are corrected during the evaluation.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *10,000 to < 20,000*

[4] *< 500*

6.30 The submission estimated the market growth using the historical data from 2016 to 2021, which was reasonable. However, the submission made several calculation errors for the script estimates:

- The average market growth per year for the period 2016-2020 was calculated using only two data points (scripts of 2016 and 2020), instead of utilising scripts numbers for each of the years to calculate the annual growth rate and then the

average for the period.

- The more accepted method for calculating market growth is fitting a regression line over the historical data and using the estimates to predict the future market. Using this method, the predicted number of scripts was substantially smaller, e.g., the forecasting at year 6 (or 2027) using the regression-based method was approximately 50% of the year 6 estimates used in the submission.
- For the financial year of 2021, the submission used the Lucrin Paediatric scripts for 2020 and only for two PBS items of 11944P and 11960L. However, the total of scripts should include PBS items of 10268T (initiation) and 10255R (continuation). The correct (estimated) total of scripts for the financial year of 2021 should be 1,206 (initiation) and 1,895 (continuation), rather than 552 (initiation) and 859 (continuation) used in the submission. Due to this error, the submission underestimated the number of scripts for Eligard 6 month for the period 2022-2027. These predicted scripts were used to calculate the financial impacts and were substantially lower than the predicted scripts used to estimate the market growth rate (Table 10 above).

6.31 The estimated scripts for Eligard 6 month are shown in Table 11.

Table 11: Estimation of number of prescriptions

		2022	2023	2024	2025	2026	2027
A	**Predicted number of scripts based on the historical data**						
A1	Predicted number of scripts – initiation (in the submission)	696	876	1,104	1,391	1,753	2,209
	Corrected	1,522	1,921	2,425	3,061	3,864	4,877
A2	Predicted number of scripts – continuation (in the submission)	1,039	1,258	1,522	1,841	2,228	2,696
	Corrected	2,284	2,753	3,319	4,001	4,823	5,813
A3	Predicted number of scripts – total	1,735	2,134	2,626	3,233	3,981	4,905
	Corrected	3,806	4,675	5,744	7,062	8,686	10,690
B	**Total script numbers of Eligard 6 month**						
B1	Total script numbers – initiation (in the submission)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
	Corrected	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
B2	Total script numbers – continuation (in the submission)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
	Corrected	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
B3	Total script numbers – total (in the submission)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
	Corrected	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]

Source: Table 4-4, p108 of the submission; Financial estimate spreadsheet of submission, 'Eligard - Leuprorelin - CPP - Financial Estimates - Base Case - 28 Feb 2022' and during the evaluation

Note: the submission made a calculation error resulting to a substantially lower script estimates as explained in 6.29 above. The corrected estimations were calculated using the submission's methodology, which is based on the average growth rates of 26% for initiation, 21% for continuation, and 22% for total, but with the correct scripts of 2021 (1,206 for initiation and 1,895 for continuation, rather than 552 for initiation and 859 for continuation in the submission).

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

6.32 The submission did not use the most recently updated DPMQ for Lucrin Paediatric ($951.64). This led to an over-estimation of the PBS cost savings. The estimated financial implications of listing Eligard 6 month are shown in Table 12.

Table 12: Estimated net cost of Eligard 6 month to the PBS/RPBS

	2022	2023	2024	2025	2026	2027
Estimated change in number of scripts and PBS/RPBS cost by Lucrin Paediatric						
Total scripts number	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Corrected	-[redacted][1]	-[redacted][1]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
PBS/RPBS cost	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Corrected	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted]	-$[redacted]	-$[redacted]
Patient copayment	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Corrected	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
PBS/RPBS cost net copayment	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Corrected	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Estimated number of scripts and PBS/RPBS costs for Eligard 6 month						
Total script numbers	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Corrected	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
PBS/RPBS cost	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Corrected	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Patient co-payment	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Corrected	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
PBS/RPBS cost net co-payment	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Corrected	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net financial impact						
Net cost PBS/RPBS	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Corrected	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]

Source Table 4-6, p110 of the submission; Financial estimate spreadsheet of submission, 'Eligard - Leuprorelin - CPP - Financial Estimates - Base Case - 28 Feb 2022' and during the evaluation, with calculation errors corrected and updated Lucrin Paediatric price

The redacted values correspond to the following ranges:

[1] *<500*

[2] *500 <5,000*

[3] *$0 to < $10 million*

6.33 The cost to the PBS/RPBS of listing Eligard 6 month was estimated by the submission to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing. This would result in a net cost saving of $0 to < $10 million in the first 6 years of listing due to the difference in price between Lucrin Paediatric and Eligard 6 month. After correction of the calculation error and adding the updated price of Lucrin Paediatric, the estimated cost to the PBS/RPBS of listing Eligard 6 month would be approximately $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing. This results in a net cost saving of $0 to < $10 million in the first 6 years of listing. After correction, the estimated PBS/RPBS cost of Eligard 6 month was substantially larger, and the cost savings were smaller than the submission's estimates. This was due to the difference in script estimates and the reduction of the price of Lucrin Paediatric as of February 2022.

6.34 The utilisation and financial were uncertain for two reasons:

- The predicted total number of scripts for the CPP market is uncertain as it is driven by an unreasonable method of market growth estimate (see above).
- The uptake rates of Eligard 6 month were assumed and not justified in the submission, especially when the market dynamics with two alternative treatments (Lucrin Paediatric and Diphereline) might play out differently from a market with one alternative (Lucrin Paediatric), presented by the submission.

6.35 The main source of uncertainty for the financial estimates presented were the estimated market growth rate (based on historical data of Lucrin Paediatric use) and uptake rates of Eligard 6 month. The ESC advised that the methods used to derive the utilisation and financial estimates and the structure of the estimates model were reliable for decision-making. The ESC advised that minor updates to the calculations used to derive the estimates should be considered as detailed in table 10. The ESC noted that sensitivity analyses were presented to assess the level of uncertainty of the estimated market growth rate. The results of the sensitivity analysis are shown in Table 13. However, given the requested price of Eligard 6 month for CPP, the listing remains cost saving under all scenarios.

Table 13: Results of sensitivity analysis

Net impact for the health budget	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026	Year 6 2027	Year 1-6 2022-27
Base case in the submission	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]
Higher uptake rate	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]
	100%	71%	41%	36%	17%	18%	29%
Calculated during the evaluation (corrected formula, DPMQ for Lucrin Paediatric = $951.64)							
Base case (corrected)	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]
Higher uptake rate	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]
	100%	71%	41%	36%	17%	18%	27%
Alternative market growth estimates – linear	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]
	83%	74%	69%	64%	58%	51%	59%

Source: Table 4-9 & Table 4-10, p 113-114 of the submission; Financial estimate spreadsheet of submission, 'Eligard - Leuprorelin - CPP - Financial Estimates - SA1 - (Final)'

The redacted values correspond to the following ranges:

[1] $0 to < $10 million

Quality Use of Medicines

6.36 The submission stated that the Sponsor will support the reimbursed supply of Eligard 6 month for CPP in Australia through a range of Quality Use of Medicines (QUM) initiatives including writing to impacted healthcare professionals explaining the CPP indication. The Sponsor also committed to making available a video and collateral material on how to mix and administer Eligard 6 month.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of Eligard 6 month for the treatment of CPP on a cost-minimisation basis to Lucrin Paediatric (leuprorelin 3-month). In making this recommendation, the PBAC considered that Eligard 6 month was non-inferior in effectiveness and safety to Lucrin Paediatric and Diphereline (triptorelin) for the treatment of CPP.

7.2 The PBAC considered that the equi-effective doses over a 1-year period were:

- 2 injections of Eligard 6 month (45 mg) ≡ 4 injections of Lucrin Paediatric
- 2 injections of Eligard 6 month (45 mg) ≡ 2 injections of Diphereline (22.5 mg)

7.3 The PBAC accepted Lucrin Paediatric as the primary comparator on the basis that it is pharmacologically the same with the same mode of action as Eligard 6 month and is the only leuprorelin acetate product PBS listed for the treatment of CPP. The PBAC accepted Diphereline as a supplementary comparator, noting that it is used to treat the same indication and has the same dose frequency as Eligard 6 month.

7.4 The PBAC noted that the submission was based on a naïve indirect comparison consisting of three open label studies and one extension study. The PBAC noted that due to the small sample size, the values could fluctuate widely, and considered that the comparative conclusion based on the observed trends may be uncertain. However, the PBAC considered that the clinical place of GnRH analogues in the treatment of CPP was well established and considered that the evidence presented was adequate to demonstrate non-inferiority given the rarity of the condition and in the context of the established clinical place of these therapies. For this reason, based on the evidence presented, the PBAC considered that Eligard 6 month is likely to be of similar comparative efficacy to Lucrin Paediatric and Diphereline for the treatment of CPP.

7.5 The PBAC noted the submission's claim that Eligard 6 month addressed an unmet clinical need in patients with CPP because it provides longer lasting treatment compared to Lucrin Paediatric; is administered less frequently compared to Lucrin Paediatric; provides an alternative leuprorelin acetate depot product for children with CPP in case of medication shortages on the PBS; and is administered by a less painful subcutaneous injection compared to Lucrin Paediatric which is an intramuscular injection. Further, the PBAC noted that there are no PBS listed formulations of leuprorelin that can be administered 6 monthly. The PBAC noted that Eligard 6 month has a longer treatment duration and frequency of administration compared to Lucrin Paediatric and considered while the clinical need for additional treatment options was low, some patients using leuprorelin may experience a modest benefit from less frequent injections. However, the PBAC considered that the submission claim of less injection site pain was not adequately supported by the trial data: injection site pain was reported at 31% in TOL2581A

(Eligard 6 month) compared to 19% and 33% in Lee 2012 and Lee 2104 (Lucrin Paediatric).

7.6 The PBAC noted that the number of adverse events appeared to be unfavourable to Eligard 6 month compared to Lucrin Paediatric in the naïve treatment arm, however, was favourable to Eligard 6 month when comparing to the Lee 2014 extension, noting that the patients in the Lee 2014 were treatment experienced. The PBAC considered that, given the high risk of bias of all the included studies and that they were all single arm studies, the comparison of safety was uncertain; however, given the established risk/benefit profile of GnRH analogues, considered the claim of non-inferior comparative safety was reasonable.

7.7 The PBAC recalled its July 2021 advice that the differences in age ranges between triptorelin and leuprorelin in the registration studies were unlikely to substantially impact clinical practice and that it was reasonable for the restrictions to reflect the upper subject age ranges in the TGA registration studies. On this basis the PBAC recommended that Eligard 6 month be used in patients who had symptom onset prior to their 8th birthday (girls) or 9th birthday (boys), and that treatment could be continued up until their 10th birthday (girls) or 11th birthday (boys), consistent with the restriction of Lucrin Paediatric for CPP.

7.8 The PBAC considered that the utilisation and financial estimates were uncertain for two reasons:

- The predicted total number of scripts for the CPP market was uncertain, driven by the method of market growth estimate.
- The uptake rates of Eligard 6 month were assumed and not justified in the submission.

However, given that the annual cost of Eligard 6 month at the requested price for CPP was less than the cost of alternative gonadotropin-releasing hormone (GnRH) analogues, the PBAC considered the listing was likely to be cost saving as it would only replace more expensive alternatives.

7.9 The PBAC noted that both Diphereline and Lucrin Paediatric are administered as intramuscular injections whereas Eligard 6 month is administered as a subcutaneous injection. The PBAC noted that the Sponsor had committed to educational and QUM activities to support clinicians with the listing of Eligard 6 month.

7.10 The PBAC advised that Eligard 6 month is not suitable for prescribing by nurse practitioners, noting that leuprorelin cannot currently be prescribed by nurse practitioners for the treatment of CPP.

7.11 The PBAC recommended that the Early Supply Rule should apply to Eligard 6 month as it currently applies to Lucrin Paediatric.

7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Eligard 6 month is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Lucrin Paediatric, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.13 PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
LEUPRORELIN					
leuprorelin acetate 45 mg modified release injection [1 syringe] (&) inert substance diluent [1 syringe], 1 pack	NEW	1	1	0	Eligard 6 month
Restriction Summary 6425 / Treatment of Concept: 6425					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Restricted benefit				
	Condition: Central precocious puberty				
	Indication: Central precocious puberty				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	Must be treated by a paediatric endocrinologist; or Must be treated by an endocrinologist specialising in paediatrics				
	AND				
	Population criteria:				
	Patient must be of an age that is prior to their 10th birthday if female; or				
	Patient must be of an age that is prior to their 11th birthday if male				
	AND				
	Population criteria:				
	Patient must have had onset of signs/symptoms of central precocious puberty prior to their 8th birthday if female; or				

	Patient must have had onset of signs/symptoms of central precocious puberty prior to their 9th birthday if male

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
LEUPRORELIN					
leuprorelin acetate 45 mg modified release injection [1 syringe] (&) inert substance diluent [1 syringe], 1 pack	NEW	1	1	0	Eligard 6 month
Restriction Summary 12351 / Treatment of Concept: 12351					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Restricted benefit				
	Condition: Central precocious puberty				
	Indication: Central precocious puberty				
	Treatment Phase: Continuing treatment with this drug, or, switching gonadotropin releasing hormone analogue therapy				
	Clinical criteria:				
	Must be treated by a medical practitioner identifying as one of: (i) a paediatric endocrinologist, (ii) an endocrinologist specialising in paediatrics; or Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion				
	AND				
	Treatment criteria				
	Patient must be undergoing continuing treatment with a gonadotropin releasing hormone analogue initiated through the PBS for this PBS indication				

8.2 Flow on changes to the wording of the population criteria to the current initial listing for Lucrin Paediatric (PBS item code: 11960L):

~~Remove~~	**Population criteria:**
~~Remove~~ *Insert New PC1*	~~Patient must be aged 10 years or younger (girls) or 11 years or younger (boys)~~ *Patient must be of an age that is prior to their 10th birthday if female; or*
Insert New PC2	*Patient must be of an age that is prior to their 11th birthday if male*
	AND
~~Remove~~	**Population criteria:**
~~Remove~~ *Insert New PC3*	~~Patient must have had onset of signs or symptoms of central precocious puberty prior to the age of 8 years (girls) or 9 years (boys)~~ *Patient must have had onset of signs/symptoms of central precocious puberty prior to their 8th birthday if female; or*
Insert New PC4	*Patient must have had onset of signs/symptoms of central precocious puberty prior to their 9th birthday if male*

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.